ORIGINAL ARTICLE

High-resolution Mass Spectrometry Analysis of Plant-derived Components of Amrytavir Liquid having Antibiotic Effect Through Antimicrobial Activity and Anticovid Activity by the Ultra-high-performance Liquid Chromatography-Based System and its Pharmacokinetic Study with Adsorption, Distribution, Metabolism, and Excretion Computational Approach

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Abstract

The Amrytavir liquid is prepared by different plant extracts by Ayurvedic manufacturing procedure among the ingredients of Amrytavir liquid such as *Withania somnifera*, *Emblica officinalis*, *Nigella sativa*, *Oroxylum indicum*, *Gmelina arborea, Uraria picta*, *Solanum virginianum*, *Cuminum cyminum*, *Mesua ferrea*, *Cyperus rotundus, Vitis vinifera*, and *Cinnamomum verum* are major plant extracts showing antibiotic effect through antimicrobial activity which revealed by the high-resolution mass spectrometry analysis of Amritavir Liquid. The listed antibiotic compounds identified are Nitecapone, Reductiomycin, Terbufos, Dimethylthionine, Corydaline, Lahorenoic acid A, Trifloxystrobin, Pyrimethamine, Xanthoangelol C, Hydranthomycin, Penialidin C, Hapalindole O, Duloxetine, Nybomycin, Asperglaucide, Lasiodipline A, Xiamycin E, and Bucillamine. Literature reports have documented that these compounds show antimicrobial and anticovid effects. The pharmacokinetic study revealed that most of the compounds are water soluble which facilitates easy administration. It is also revealed that most of the antibiotic compounds show high intestinal absorption which facilitates rapid drug action over the human body system.

Key words: Amrytavir liquid, antibiotic activity, Ayurvedic medicine, high-resolution mass spectrometry, pharmacokinetic study

INTRODUCTION

Ayurveda system of medicine is an ancient system of medicine practiced in the Indian sub-continent for many decades. In the present study, Amrytavir liquid is prepared by selecting the plant products on the basis of the literature mentioned in Ayurveda. Amrytavir liquid is an Ayurvedic liquid dosage form manufactured in AMIL Pharmaceuticals

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(INDIA) Ltd., A-13/2, Naraina Industrial Area, Phase-1, New Delhi-110028 for the purpose of a clinical trial over COVID-19 subjects and this Amrytavir liquid is analyzed by high-resolution mass spectrometry (HRMS) through an ultra-high-performance liquid chromatography (UHPLC)-based system. Amrytavir liquid is produced by 13 plant products and honey [Table 1].

The Amrytavir liquid is prepared by different plant extracts by Ayurvedic manufacturing procedure among the ingredients of Amritavir liquid such as *Withania somnifera*, *Emblica officinalis*, *Nigella sativa*, *Oroxylum indicum*, *Gmelina arborea*, *Uraria picta*, *Solanum virginianum*, *Cuminum cyminum*, *Mesua ferrea*, *Cyperus rotundus*, *Vitis vinifera*, and *Cinnamomum verum*. *W. somnifera* root extract shows inhibitory activity against bacterial activated autoimmune diseases.[1] *E. officinalis* has antibacterial and antifungal activities against *Staphylococcus aureus*, *Salmonella* Typhi, *Bacillus subtilis*, *Shigella dysenteriae*, and *Bacillus megaterium*.[2] *N. sativa* exerted powerful antibacterial effects against both Gram-positive (POS) and Gram-negative (NEG) species.[3] *O. indicum* bark shows anti-bacterial against both Gram-POS and Gram-NEG species.[4] *G. arborea* has antibacterial activities on human pathogens such as *B. subtilis*, *S. aureus,* and *Pseudomonas aeruginosa*.[5] *S. virginianum* showed antimicrobial properties.[6] *C. cyminum* oil has antibacterial effect.[7] *M. ferrea* whole flowers exhibited antibacterial effect against various strains of bacteria.[8] *C. rotundus* essential oil showed antibacterial activity against foodborne pathogens.[9] *V. vinifera* showed high antibacterial action against *Salmonella* Typhimurium and *Escherichia coli*.[10] *C. verum* oil has strong antimicrobial action against *Streptococcus iniae* infection.[11]

As all the plant ingredients of Amrytavir liquid formulation exhibit potential antimicrobial role, the formulation is yet to be explored for its antimicrobial profile. In the present study, UHPLC-based HRMS method is used to identify various bioactive compounds of the ingredients of Amrytavir liquid. The antibiotic compounds analyzed by HRMS were further subjected to pharmacokinetic investigation using the SWISS adsorption, distribution, metabolism, and excretion (ADME) website.

MATERIALS AND METHODS

About instrument

The High-Resolution Accurate Mass Spectrometry System instrument was used with the Model name Orbitrap Eclipse Tribrid Mass Spectrometer developed by Thermo Fischer Scientific. The DionexUltiMate 3000 RS UHPLC system was employed for detailed phytochemical analysis of small molecules, whereas a distinct solvent compound was utilized for conducting the antibacterial analysis.

Medicine preparation for HRMS analysis

Amrytavir liquid is a traditional formulation prepared by a self-generated hydro-alcohol extraction process and it is prepared using ingredients mentioned in Table 1. This liquid dosage form of Amrytavir in 2 mL quantity was used for HRMS analysis to find the compounds which are having antibacterial activity.

Solvent preparation of HPLC column

Solvent A: 100% Water + 0.1% Formic Acid. Solvent B: 80% Acetonitrile + 0.1% Formic Acid. Solvent C: 100% Methanol + 0.1% Formic Acid. The three solvents A, B, and C are used in columns. The Column detail is the Hypersil GOLD™ C18 Selectivity HPLC Column, Particle size 1.9 µm with diameter 2.1 mm, Length 100 mm. All the analyses were performed by the default parameters of "Compound discoverer 3.2.0.421" using online databases.

UHPLC-Q-TOF-MS/MS was used to examine the Amrytavir liquid metabolite profile. The Thermo Compound Discoverer 3.3.2.31 was used for all of the analysis, with default settings and Online Databases, and mzLogic. The chemicals were identified based on fragment patterns produced by ChemSpider (formula or precise mass) and mzCloud (ddMS2).

ADME study

The Amrytavir liquid antibiotics extracted from HRMS Analysis were subjected to ADME prediction. ADME is extremely useful for evaluating the pharmacodynamic characteristics of a prospective medicinally useful synthetic molecule. SWISS ADME website (https://www.swissadme.ch),[12] users can create their own drug or ligand molecules, as well as add Canonical SMILES data from PubChem and do parameter analysis such as lipophilicity, water solubility, polarity, pharmacokinetics, i.e., blood–brain barrier (BBB) penetrant, GI-Absorption level, CYP2D6-cytochrome P-450 2D6 inhibitors, and plasma protein binding (PPB) level.

RESULTS

In Amrytavir liquid, the antibiotic compounds were identified by UHPLC-MS. The total ion chromatogram and extracted ion chromatograms for some of the significantly identified different antibacterial drugs together with the base peak chromatogram of the sample acquired by NEG and POS ion mode along their molecular structure and ion chromatogram are mentioned in Figures 1 and 2. The compound structure of the major antimicrobial compounds of Amrytavir liquid is mentioned in Figure 3.

Table 1: Composition of Amrytavir liquid

Name in traditional Ayurvedic medicine	Part used	Botanical name	Textual reference	Quantity
Aqueous extract derived from				
Kalmegh	Aerial Part	*Andrographis paniculata*	API-I, Vol. VIII, Pg. 101	500 mg
Bhuiamla	Whole Plant	*Phyllanthus amarus*	AFI-III, Pg. 433	500 mg
Vasa	Leaf	*Adhatoda vasica*	API-I, Vol. I, Pg. 122	500 mg
Ashwagandha	Root	*Withania somnifera*	API-I, Vol. I, Pg. 15	500 mg
Tulsi	Whole Plant	*Ocimum sanctum*	API-I, Vol. II, Pg. 162	300 mg
Triphala	Processed	An equi mix of Fr. P. of *Terminalia chebula*+*Emblica officinalis*+*Terminalia bellirica*	AFI-I, Pg. 110	200 mg
Oils				
Kalaunji	Seed Processed	*Nigella sativa* oil	API-I, Vol. I, Pg. 119	10 mg
Tulsi	Whole Plant Processed	*Ocimum sanctum* oil	API-I, Vol. II, Pg. 162	5 mg
Lavang (Clove)	Flower Bud Processed	*Syzygium aromaticum* oil	API-I, Vol. VI, Pg. 212	2 mg
Powders				
Kapoor	Leaf Processed	*Cinnamomum camphora* ext.	API-I, Vol. VI, Pg. 210	2 mg
Pudina	Aerial Part Processed	Mentha Sps. ext.	API-I, Vol. VI, Pg. 216	2 mg
Arishta				
Draksharishta	Processed	*Classical Ay. Preparation*	AFI-I, Pg. 15	2.5 ml
Amritarishta	Processed	*Classical Ay. Preparation*	AFI-I, Pg. 6	2.5 ml
Madhu	Processed	*Honey*	API-I, Vol. VI, Pg. 214	2 gm

A summary of all the compounds of Amrytavir liquid has been discovered as an antimicrobial which includes the chemical name, constituent group, molecular formula, computed molecular weight (m/z), mass error (ppm), retention period, and peak areas in the NEG and POS ion modes. The list of antibacterial compounds is Nitecapone, Reductiomycin, Terbufos, Dimethylthionine, Corydaline, Lahorenoic acid A, Trifloxystrobin, Pyrimethamine, Xanthoangelol C, Hydranthomycin, Penialidin C, Hapalindole O, Duloxetine, Nybomycin, Asperglaucide, Lasiodipline A, Xiamycin E, and Bucillamine (BUC) [Table 2].

Literature reports have documented that these compounds show antimicrobial effects. Nitecapone is a novel catechol-*O*-methyltransferase inhibitor with potent antioxidant properties.[13] Nitecapone shows antioxidant properties with peroxyl radical scavenging activity.[14] Reductiomycin shows antitumor antibiotic activity.[15] Crude extract of *Streptomyces* species one of the actinomycetes containing reductiomycin shows broad-spectrum antibacterial activity.[16] Pesticides of Terbufos show antibacterial activity through phosphorylation of H2AX (γH2AX) caused by DNA double-strand breaks.[17] Terbufos (S-t-butylthiomethyl-O,O-diethyl phosphorodithioate) shows anticancer activity through Reactive Oxygen Species Mediate Apoptosis in mouse testicular cell line.[18] Azure A is an asymmetrical dimethylthionine belonging to the phenothiazinium group and shows anticancer activity along with antimalarial effects.[19] The crude extract of *Corydalis yanhusuo* W. T. Wang (Papaveraceae) constitutes that corydaline is potent anti-inflammatory, anti-depressive, and anticancer effects. PTGS2, PTGS1, KCNH2, SCN5A, RXRA, CAMKK2, NCOA2, and ESR1 expression may be regulated by corydalmine, enabling a possible therapy for pain, stomach ulcers, and inflammation.[20] Lahorenoic acid A isolated from biocontrol strain *Pseudomonas aurantiaca* PB-St2 has antibacterial nature against mycobacteria and other Gram-POS bacteria[21] also used for sustainable agriculture and pharmaceuticals.[22] Trifloxystrobin is used as broad-range antifungal activity against *Macrophomina phaseolina*.[23] Pyrimethamine along with sulfadoxine reduces the risk of Malaria.[24] A geranylated chalcone called xanthoangelol has antibacterial properties against Gram-POS bacteria such as methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecium*, and *Enterococcus faecalis* at low micromolar concentrations by disturbing membrane potentially cause pore formation which out-turn to cell lysis.[25] Hydranthomycin a bioactive compound isolated from *Streptomyces* spp. 201 shows inhibition against dominant soil-borne phytopathogens such as *Fusarium oxysporum* Schlecht, *Fusarium moniliforme* Sheldon, *Fusarium semitectum*, *Fusarium solani* (Martius) Sacc, and *Rhizoctonia solani* Kuehn.[26] Penialidin C derived from *Penicillin* spp. has antimycobacterial activity against *Mycobacterium smegmatis*.[27] Hapalindole O an alkaloid has antimicrobial activity against various fungal and bacterial strains, such as *Pseudomonas syringae*, *E. coli*, *Bacillus*

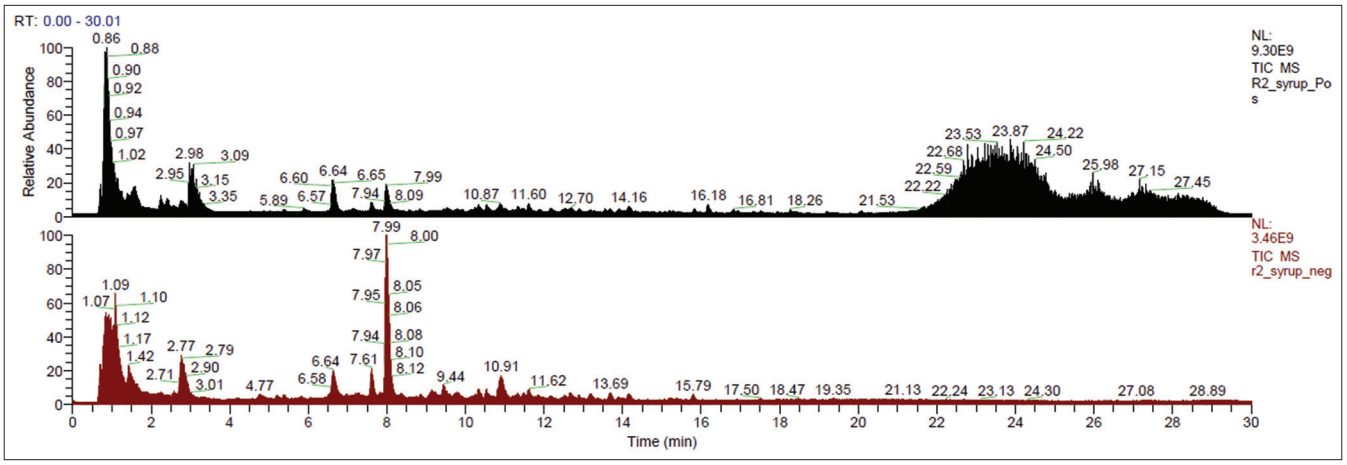


Figure 1: Total ion chromatogram obtained by UHPLC-TOF-MS analysis of the Amrytavir liquid sample in positive and negative ion mode

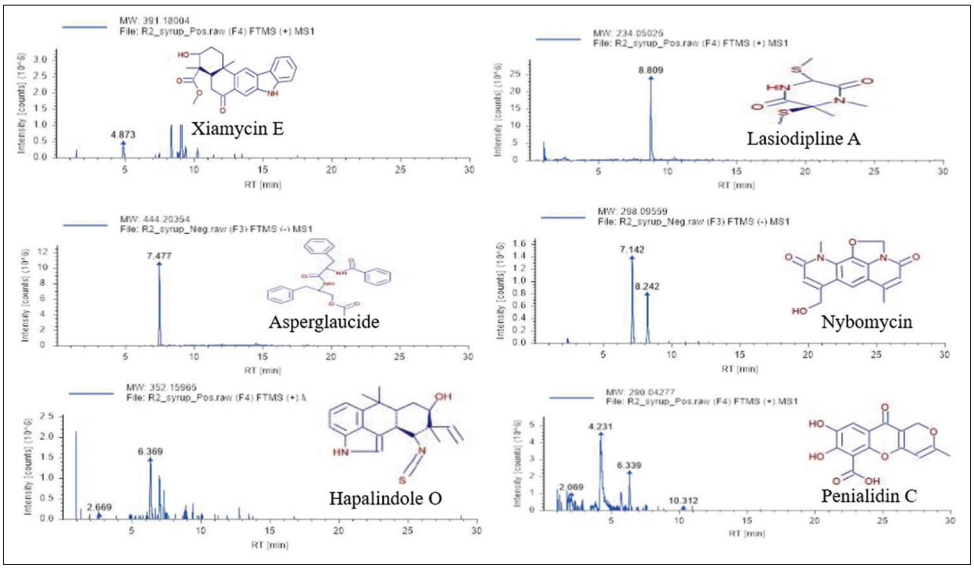


Figure 2: Separate ion chromatography of major antibiotics present in Amrytavir liquid

cereus, *Pseudomonas putida*, *Salmonella* spp., *F. oxysporum*, *Cercospora canescens,* and *Colletotrichum dematium*.[28] Duloxetine an anti-depressive agent shows an antimicrobial effect against intestinal gut microbiota.[29] *E. coli* and *E. faecalis*, two of the most common bacterial pathogens that cause catheter-associated urinary tract infections, are inhibited by the antidepressant medicine duloxetine.[30] Nybomycin an old antibiotic is active against quinolone-resistant *S. aureus* strains with mutated *gyrA* genes.[31] Asperglaucide isolated from Vietnamese medicinal plant *Psychotria reevesi*i Wall. (Rubiaceae) shows antibacterial activities against *S. aureus*, *P. aeruginosa*, *Shigella sonnei*, and *Shigella flexneri*.[32] Lasiodipline A composition of an endophytic fungal isolate, *Lasiodiplodia pseudotheobromae* IBRL OS-64 residing in leaves of a medicinal herb, *Ocimum sanctum* Linn has antimicrobial effect against three Gram-POS bacteria (MRSA ATCC 33591, *S. aureus*, and *Streptococcus mutans*).[33] A number of microorganisms, including MRSA and vancomycin-resistant *E. faecalis*, are susceptible to the moderate to potent antibacterial effects of xiamycins.[34] BUC worked as a potential drug for COVID-19 treatment.[35]

ADME properties study

The antibiotics studied for ADME properties. The pharmacological properties of all 18 antibiotics were predicted, including aqueous solubility, ability to cross the BBB, CYP2D6 inhibition, human-intestinal absorption level, and ability to bind to plasma proteins. From ADME pharmacokinetic study, it is found that the maximum compounds are water soluble in nature. The antibiotic compounds, i.e., Corydaline, Lahorenoic acid A, Pyrimethamine, and Duloxetine are capable to cross blood–brain barrier and these compounds are easily transported through neurons. The antibiotics such as Corydaline, Hydranthomycin, Duloxetine, Asperglaucide, and Xiamycin E are CYP2D6-cytochrome P-450 2D6 inhibitors. These antibiotics can be used to treat depressive and panic

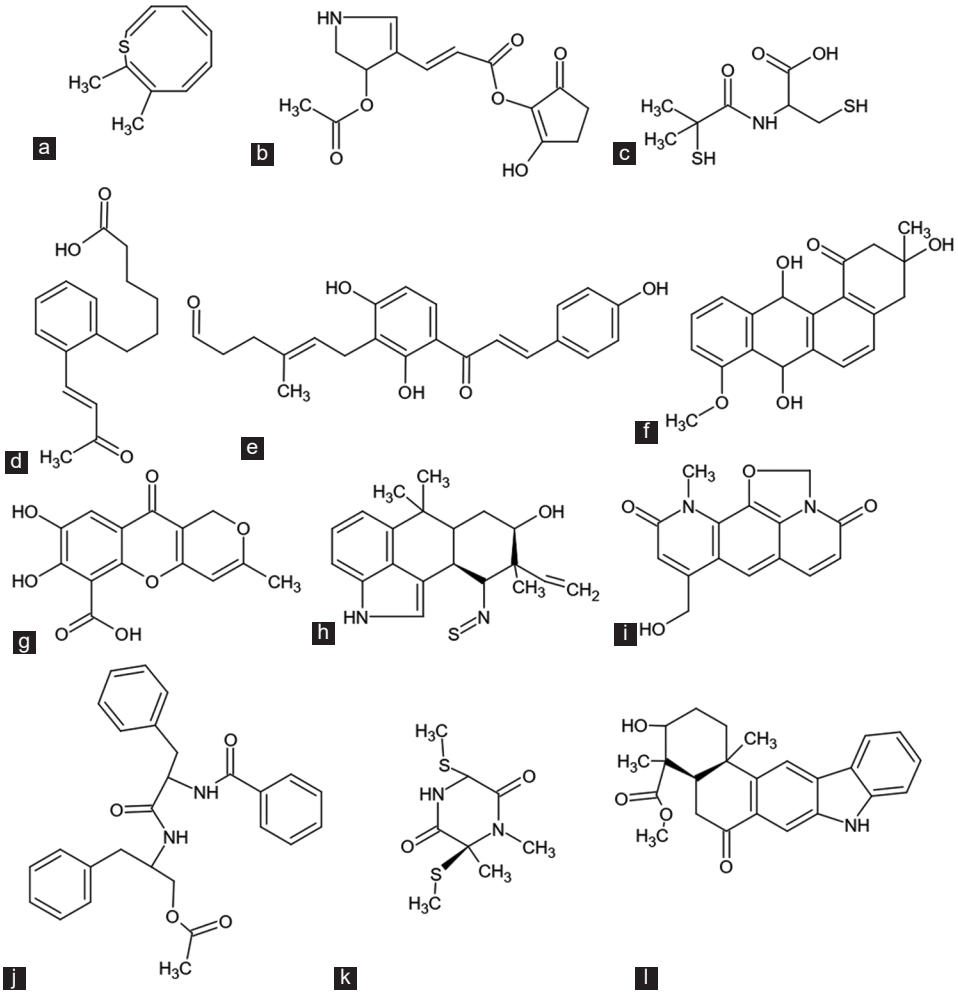
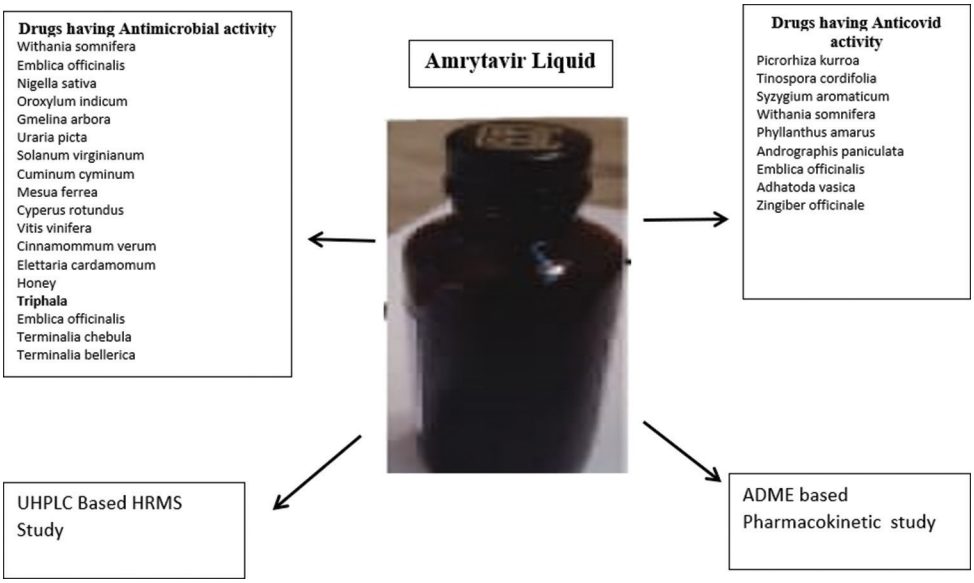


Figure 3: Major molecular structure of antimicrobial compounds present in Amrytavir Liquid. (a) Dimethylthionine, (b) Reductiomycin, (c) Bucillamine, (d) Lahorenoic acid A, (e) Xanthoangelol C, (f) Hydranthomycin, (g) Penialidin C, (h) Hapalindole O, (i) Nybomycin, (j) Asperglaucide, (k) Lasiodipline A, (l) Xiamycin E



Graphical abstract showing different plant ingredients activity of Amrytavir Liquid and studies conducted.

disorders in the future. All the antibiotic compounds except BUC show high absorptions in the gastrointestinal track and are easily take part in metabolism. The antibiotics such as Dimethylthionine, Hydranthomycin, Duloxetine,

Table 2: Major compounds identified by UHPLC-TOF-MS analysis through positive and negative ion mode, showing molecular formula, molecular weight, calculated delta mass error (ppm), retention time values, the peak area of Amrytavir Liquid sample in negative and positive ion mode

Compound name	Molecular formula	Molecular weight	Delta mass (ppm)	Retention time (min)	Area negative	Area positive
Dimethylthionine	$C_{10}H_{12}S$	164.0665	3.41	1.027		12611122
Reductiomycin	$C_{14}H_{15}NO_6$	293.0903	1.15	1.073		1.62000008
Terbufos	$C_9H_{21}O_2PS_3$	288.0427	−4.81	1.079		7030067
Nitecapone	$C_{12}H_{12}NO_6$	266.0665	0.07	1.091	60099143	
Bucillamine	$C_7H_{13}NO_3S_2$	223.0328	−4.15	1.101	6570574	
Corydaline	$C_{22}H_{27}NO_4$	369.1958	4.82	1.376		9800366
Lahorenoic acid A	$C_{16}H_{20}O_3$	260.1402	−4.09	1.559	6387984	
Trifloxystrobin	$C_{20}H_{19}F_3N_2O_4$	408.1308	2.82	1.699	50746809	
Pyrimethamine	$C_{12}H_{13}ClN_4$	248.0822	−2.91	1.905	18786695	
Xanthoangelol C	$C_{22}H_{22}O_5$	366.1462	−1.45	5.302	8673578	
Hydranthomycin	$C_{20}H_{20}O_5$	340.13	−3.1	5.886	8805238	
Penialidin C	$C_{14}H_{10}O_7$	290.0428	0.41	6.349		10527918
Hapalindole O	$C_{21}H_{24}N_2OS$	352.1597	−3.63	6.359		9179704
Duloxetine	$C_{18}H_{19}NOS$	297.1181	−2.17	6.744		5925919
Nybomycin	$C_{16}H_{14}N_2O_4$	298.0956	0.8	7.147	87146830	
Asperglaucide	$C_{27}H_{28}N_2O_4$	444.2035	−3.09	7.474	49370649	
Lasiodipline A	$C_8H_{14}N_2O_2S_2$	234.0503	2.48	8.805		1.050000008
Xiamycin E	$C_{24}H_{25}NO_4$	391.18	4.3	9.093		14636870

Asperglaucide, and Xiamycin E are bind agents to plasma-protein and easily transported in blood. Plasma protein binding (PPB) plays a crucial role in drug therapy, as it can significantly influence both the pharmacokinetics and pharmacodynamics of a drug.

DISCUSSION

Amrytavir liquid contains the various plant products as ingredients, however, the following plant ingredients, i.e., *W. somnifera*, *E. officinalis*, *N. sativa*, *O. indicum*, *G. arborea*, *U. picta*, *S. virginianum*, *C. cyminum*, *M. ferrea*, *C. rotundus*, *V. vinifera*, *C. verum* possessing antibiotic compounds, i.e., Nitecapone, Reductiomycin, Terbufos, Dimethylthionine, Corydaline, Lahorenoic acid A, Trifloxystrobin, Pyrimethamine, Xanthoangelol C, Hydranthomycin, Penialidin C, Hapalindole O, Duloxetine, Nybomycin, Asperglaucide, Lasiodipline A, Xiamycin E, BUC which is found in the analysis of HRMS-UHPLC system. Major molecular structure of antimicrobial compounds present in Amrytavir Liquid is represented in Figure 3. The molecular formula, molecular weight, delta mass (ppm), retention time, area NEG, and area POS of each antibiotic compound are identified and mentioned in Table 2. The total ion chromatography and the separate ion chromatography of each antibiotic compound are represented in Figures 1 and 2. It is noticed that antimicrobial activity which is found by the HRMS analysis of Amritavir Liquid has having broad-spectrum antibiotic effect.

As mentioned in Table 3, ADME properties of antibiotic compounds represent solubility level-water solubility level (soluble/moderate soluble), BBB level – BBB penetrant (Yes/No), CYP2D6-cytochrome P-450 2D6 inhibitors (decreased metabolism of substrate drug, Yes/No), absorption level-gastro-intestinal absorption level (Yes/No), PPB level-PPB (the strength with which drugs bind to blood proteins in blood plasma Yes/No); it is found that in the pharmacokinetic study that most of the compounds are water soluble which facilitates better administration and also noticed that most of the antibiotic compounds show rapid intestinal absorption which facilitates better drug performance over human body system.

The antibiotic compounds specifically, i.e., Corydaline, Lahorenoic acid A, Pyrimethamine, Duloxetine, Asperglaucide are able to cross blood–brain barrier, therefore, these compounds are easily transported through neurons and produces synergistic drug action over the human body system. Antibiotics such as Corydaline, Hydranthomycin, Duloxetine, Asperglaucide, and Xiamycin E act as CYP2D6 (cytochrome P450 2D6) inhibitors and have been reported to exhibit notable antidepressant activity.

The antibiotics such as Dimethylthionine, Hydranthomycin, Duloxetine, Asperglaucide, and Xiamycin E are binding agents to plasma-protein and easily transported in blood. With

Table 3: Adsorption, distribution, metabolism, and excretion properties of antibiotic compounds represents solubility level-water solubility level (soluble/moderate soluble), BBB level – BBB penetrant (Yes/No), CYP2D6-cytochrome P-450 2D6 inhibitors (Decreased metabolism of substrate drug, Yes/No), Absorption level- Gastro-intestinal absorption level (Yes/No), PPB level-plasma protein binding (the strength with which drugs bind to blood proteins in blood plasma Yes/No)

S. No.	Compound name	Water solubility level	BBB level	CYP2D6 inhibitor	Absorption level GI track	PPB level
1.	Dimethylthionine	Soluble	No	No	High	Yes
2.	Reductiomycin	Very soluble	No	No	High	No
3.	Terbufos	Soluble	No	No	High	No
4.	Nitecapone	Soluble	No	No	High	No
5.	Bucillamine	Very soluble	No	No	Low	No
6.	Corydaline	Moderately soluble	Yes	Yes	High	No
7.	Lahorenoic acid A	Soluble	Yes	No	High	No
8.	Trifloxystrobin	Moderately soluble	No	No	High	No
9.	Pyrimethamine	Soluble	Yes	No	High	No
10.	Xanthoangelol C	Moderately soluble	No	No	High	No
11.	Hydranthomycin	Soluble	no	Yes	High	Yes
12.	Penialidin C	Soluble	No	No	High	No
13.	Hapalindole O	Moderately soluble	No	No	High	No
14.	Duloxetine	Moderately soluble	Yes	Yes	High	Yes
15.	Nybomycin	Very soluble	No	No	High	No
16.	Asperglaucide	Moderate soluble	No	Yes	High	Yes
17.	Lasiodipline A	Very soluble	No	No	High	No
18.	Xiamycin E	Moderately soluble	No	Yes	High	Yes

these findings, the Amrytavir liquid which is a natural product showing antibiotic effect, rapid intestinal absorption, some of the compounds are easily transported through neurons and produce synergistic drug action over human subjects and CYP2D6-cytochrome P-450 2D6 inhibitors are responsible for body metabolism and they are anti-depressive drugs.

CONCLUSION

Amrytavir liquid is a natural product and is prepared by different Ayurvedic plant extracts for the purpose of antibiotic effect. Antimicrobial activity which is revealed by the HRMS analysis of Amritavir Liquid is showing broad spectrum antibiotic effect. The pharmacokinetic study revealed that most of the compounds are water soluble which facilitates easy administration. It is also revealed that most of the antibiotic compounds show high intestinal absorption which facilitates rapid drug action over the human body system.

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